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REVIEW ARTICLE

NIOSOMES: THE UNIQUE VESICULAR DRUG CARRIERS

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ABSTRACT

Drug targeting is the ability to direct a therapeutic agent specifically to desired site of action with little or no interaction with nontarget tissue. Niosomes are one of the best carriers for drug targeting. Niosomes are self-assembled vesicles composed primarily of synthetic surfactants and cholesterol. They are analogous in structure to the more widely studied liposomes formed from biologically derived phospholipids. Niosomes are biodegradable, relatively nontoxic, more stable and inexpensive, an alternative to liposomes. The method of preparation of niosome is based on liposome technology. The basic process of preparation is the same i.e. hydration by aqueous phase of the lipid phase which may be either a pure surfactant or a mixture of surfactant with cholesterol. After preparing niosomal dispersion, unentrapped drug is separated by dialysis centrifugation or gel filtration. Niosomes can be SUV (Small Unilamellar Vesicles), MLV (Multilamellr Vesicles) or LUV (Large Unilamellar Vesicles). Niosomal drug delivery is potentially applicable to many pharmacological agents for their action against various diseases.

Keywords: Niosomes, vesicles, sonication, fluidization.

INTRODUCTION

In the era of novel drug delivery system (NDDS) emphasis is given on spatial placement of drug for chronic conditions. Targeted delivery of anticancer and anti-infective drugs appears to be challenging but achievable task with the use of novel drug delivery systems. Different novel approaches used for delivering these drugs include liposomes, microspheres, nanotechnology, micro-emulsion, antibody-loaded drug delivery, magnetic microcapsules, implantable pumps and niosomes [1].

Niosomes or non-ionic surfactant vesicles are microscopic lamellar structures formed on admixture of non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media[2].Niosomes can be changed or modified by the incorporation of other excipients like cholesterol, into the membrane and they can possess one or more lipid bilayers encapsulating an aqueous core. A diverse range of materials have been used to form Niosomes such as sucrose ester surfactants and polyoxyethylene alkyl ether surfactants.

Niosome vesicles were prepared with the thin layer evaporation method and were physicochemically characterized. In comparison with classical formulations such as emulsions, these systems exhibit lower toxicity and permit closer control of the availability of active substances at the stratum corneum. Niosomes may act as a depot, releasing the drug in a controlled manner. The therapeutic performance of the drug molecules can also be improved by delayed clearance from the circulation, protecting the drug from biological environment and restricting effects to target cells[3]. It can also be used as vehicle for poorly absorbable drugs to design the novel drug delivery system. It enhances the bioavailability by crossing the anatomical barrier of gastrointestinal tract via transcytosis of M cells of Peyer's patches in the intestinal lymphatic tissues[4].

The niosomal vesicles are taken up by reticulo-endothelial system. Such localized drug accumulation is used in treatment of diseases, such as leishmaniasis, in which parasites invade cells of liver and spleen[5]. Some non-reticulo-endothelial systems like immunoglobulins also recognize lipid surface of this delivery system[6]. Encapsulation of various anti-neoplastic agents in this carrier vesicle has minimized drug-induced toxic side effects while maintaining, or in some instances, increasing the anti-tumour efficacy[7]. Many drugs are administered through niosomes via transdermal route to improve the therapeutic efficacy.

Niosomes provides better drug concentration at the site of action administered by oral, parenteral and topical routes. The evolution of niosomal drug delivery technology is still at the stage of infancy, but this type of drug delivery system has shown promise in cancer chemotherapy and anti-leishmanial therapy. In niosomes, the vesicles forming amphiphile is a non-ionic surfactant such as Span – 60 which is usually stabilized by addition of cholesterol and small amount of anionic surfactant such as dicetyl phosphate[8].

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TYPES OF NIOSOMES

Based on the vesicle size, niosomes can be divided into three groups:

(i) Small Unilamellar Vesicles (SUV, Size=0.025-0.05 μm),

(ii) Multilamellar Vesicles (MLV, Size=>0.05 μm),

(iii) Large Unilamellar Vesicles (LUV, Size=>0.10 μm).

Niosomes In Lieu Of Liposomes – Reasons

One of the most significant problems associated with the use of liposomes as adjuvant is the susceptibility of phospholipids to oxidative degradation in air. This requires that purified phospholipids and liposomes have to be stored and handled in an inert (e.g. nitrogen) atmosphere[9]. Phospholipid raw materials are naturally occurring substances and as such require extensive purification thus making them costly.Alternatively, phospholipids can be synthesised de novo, however this approach tends to be even more costly than using naturally occurring lipids.Because of liposomes above mentionioned drawbacks, alternative nonionic surfactants have been investigated. This involves formation of liposome-like vesicles from the hydrated mixtures of cholesterol and nonionic surfactant such as monoalkyl or dialkyl polyoxyethylene ether36. Niosomes are unilamellar or multilamellar vesicles capable of entrapping hydrophilic and hydrophobic solutes[10].From a technical point of view, niosomes are promising drug carriers as they possess greater stability and lack of many disadvantages associated with liposomes, such as high cost and the variable purity problems of phospholipids[11]. Another advantage is the simple method for the routine and large-scale production of niosomes without the use of unacceptable solvents. Cholesterol, 5-cholesten-3β-ol is used in combination with nonionic surfactant for the formation of niosomes.

Advantages of Niosomes

- Since the structure of the niosome offers place to accommodate hydrophilic, lipophilic as well as ampiphilic drug moieties, they can be used for a variety of drugs. [12]
- Niosomes exhibits flexibility in their structural characteristics (composition, fluidity and size) and can be designed according to the desired situation.
- They improve the therapeutic performance of the drug by protecting it from the biological environment and restricting effects to target cells, thereby reducing the clearance of the drug.
- Niosomes can act as a depot to release the drug slowly and offer a controlled release.
- They can increase the oral bioavailability of drugs.
- They are osmotically active and stable.
- They increase the stability of the entrapped drug.
- They can enhance the skin penetration of drugs.
- They can be made to reach the site of action by oral, parenteral as well as topical routes.
- The surfactants are biodegradable, biocompatible, and non-immunogenic.
- The niosomal dispersions in an aqueous phase can be emulsified in a non-aqueous phase to control the release rate of the drug and administer normal vesicles in external non-aqueous phase.
- Handling and storage of surfactants do not require any special conditions.
- The vesicle suspension being water based offers greater patient compliance over oily dosage forms.

METHODS OF PREPARATION OF NIOSOMES

Preparation of vesicles: The preparation methods should be chosen according to the use of niosomes, since the preparation methods influence the numbers of bilayers, size, size distribution and entrapment efficiency of the aqueous phase and the membrane permeability of the vesicles.

1. Ether injection method

This method provides a means of making niosomes by slowly introducing a solution of surfactant dissolved in diethyl ether into warm water maintained at 60°C. The surfactant mixture in ether is injected through 14-gauge needle into an aqueous solution of material. Vaporization of ether leads to formation of single layered vesicles. Depending upon the conditions used the diameter of the vesicle range from 50 to 1000 nm. [13]

2. Hand shaking method (Thin film hydration technique)

The mixture of vesicles forming ingredients like surfactant and cholesterol are dissolved in a volatile organic solvent (diethyl ether, chloroform or methanol) in a round bottom flask. The organic solvent is removed at room temperature (20°C) using rotary evaporator leaving a thin layer of solid mixture deposited on the wall of the flask. The dried surfactant film can be rehydrated with aqueous phase at 0-60°C with gentle agitation. This process forms typical multilamellar niosomes.

Thermosensitive niosomes were prepared by Raja Naresh *et al*[14] by evaporating the organic solvent at 60°C and leaving a thin film of lipid on the wall of rotary flash evaporator. The aqueous phase containing drug was added slowly with intermittent shaking of flask at room temperature followed by sonication.

3. Sonication

A typical method of production of the vesicles is by sonication of solution as described by Cable [15]. In this method an aliquot of drug solution in buffer is added to the surfactant/cholesterol mixture in a 10-ml glass vial. The mixture is probe sonicated at 60°C for 3 minutes using a sonicator with a titanium probe to yield niosomes.

4. Micro fluidization

Micro fluidization is a recent technique used to prepare unilamellar vesicles of defined size distribution. This method is based on submerged jet principle in which two fluidized streams interact at ultra-high velocities, in

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precisely defined micro channels within the interaction chamber. The impingement of thin liquid sheet along a common front is arranged such that the energy supplied to the system remains within the area of niosomes formation. The result is a greater uniformity, smaller size and better reproducibility of niosomes formed. [16]

5. Multiple membrane extrusion method

Mixture of surfactant, cholesterol and dicetyl phosphate in chloroform is made into thin film by evaporation. The film is hydrated with aqueous drug solution and the resultant suspension extruded through polycarbonate membranes, which are placed in series for upto 8 passages. It is a good method for controlling niosome size.

6. Reverse Phase Evaporation Technique (REV)

Cholesterol and surfactant (1:1) are dissolved in a mixture of ether and chloroform. An aqueous phase containing drug is added to this and the resulting two phases are sonicated at 4-5°C. The clear gel formed is further sonicated after the addition of a small amount of phosphate buffered saline (PBS). The organic phase is removed at 40°C under low pressure. The resulting viscous niosome suspension is diluted with PBS and heated on a water bath at 60°C for 10 min to yield niosomes.

Raja Naresh et al have reported the preparation of Diclofenac Sodium niosomes using Tween 85 by this method.

7. Trans membrane pH gradient (inside acidic) Drug Uptake Process (remote Loading)

Surfactant and cholesterol are dissolved in chloroform. The solvent is then evaporated under reduced pressure to get a thin film on the wall of the round bottom flask. The film is hydrated with 300 mM citric acid (pH 4.0) by vortex mixing. The multilamellar vesicles are frozen and thawed 3 times and later sonicated. To this niosomal suspension, aqueous solution containing 10 mg/ml of drug is added and vortexed. The pH of the sample is then raised to 7.0-7.2 with 1M disodium phosphate. This mixture is later heated at 60°C for 10 minutes to give niosomes. [17]

8. The "Bubble" Method

It is novel technique for the one step preparation of liposomes and niosomes without the use of organic solvents. The bubbling unit consists of round-bottomed flask with three necks positioned in water bath to control the temperature. Water-cooled reflux and thermometer is positioned in the first and second neck and nitrogen supply through the third neck. Cholesterol and surfactant are dispersed together in this buffer (pH 7.4) at 70°C, the dispersion mixed for 15 seconds with high shear homogenizer and immediately afterwards "bubbled" at 70°C using nitrogen gas. [18]

9. Formation of niosomes from proniosomes

Another method of producing niosomes is to coat a water-soluble carrier such as sorbitol with surfactant. The result of the coating process is a dry formulation. In which each water-soluble particle is covered with a thin film of dry surfactant. This preparation is termed "Proniosomes". The niosomes are recognized by the addition of aqueous phase at T > Tm and brief agitation.

T = Temperature.

Tm = mean phase transition temperature.

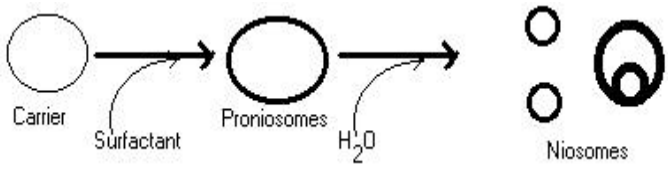

Figure 1: Formation of niosomes from proniosomes.

Blazek-Walsh A.I. et al have reported the formulation of niosomes from maltodextrin based proniosomes. This provides rapid reconstitution of niosomes with minimal residual carrier. Slurry of maltodextrin and surfactant was dried to form a free flowing powder, which could be rehydrated by addition of warm water. [19]

DIFFERENT FORMULATIONS OF NIOSOMES

1. Discomes.
2. Niosomes vesicles in water/oil systems.
3. Proniosomes.
4. Niosomal dispersions.
5. Polymer coated niosomes

Characterization of Niosomes

Size

Shape of niosomal vesicles is assumed to be spherical, and their mean diameter can be determined by using laser light scattering method[20].Also, diameter of these vesicles can be determined by using electron microscopy, molecular sieve chromatography, ultracentrifugation, photon correlation microscopy and optical microscopy and.freeze fracture electron microscopy. Freeze thawing of niosomes increases the vesicle diameter, during the cycle.

Vesicle Charge

The vesicle surface charge can play an important role in the behavior of niosomes in vivo and in vitro.[21]

Bilayerformation

Assembly of non-ionic surfactants to form a bilayer vesicle is characterised by an X-cross formation under light polarisation microscopy[22].

Numberoflamellae

This is determined by using nuclear magnetic resonance (NMR) spectroscopy, small angle X-ray scattering and electron microscopy.

Membrane rigidity

Membrane rigidity can be measured by means of mobility of fluorescence probe as a function of temperature.

Entrapment efficiency

After preparing niosomal dispersion, unentrapped drug is separated and the drug remained entrapped in niosomes is determined by complete vesicle disruption using 50% n-propanol or 0.1% Triton X-100 and analysing the resultant

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solution by appropriate assay method for the drug[23].It can be represented as :-

Entrapment efficiency (EF) = (Amount entrapped / total amount) X 100

In vitro Release Study

A method of in vitro release rate study was reported with the help of dialysis tubing[24]. A dialysis sac was washed and soaked in distilled water. The vesicle suspension was pipetted into a bag made up of the tubing and sealed. The bag containing the vesicles was then placed in 200 ml buffer solution in a 250 ml beaker with constant shaking at 25°C or 37°C. At various time intervals, the buffer was analysed for the drug content by an appropriate assay method.In another method, isoniazid-encapsulated niosomes were separated by gel filtration on Sephadex G-50 powder kept in double distilled water for 48 h for swelling[25]. At first, 1 ml of prepared niosome suspension was placed on the top of the column and elution was carried out using normal saline. Niosomes encapsulated isoniazid elutes out first as a slightly dense, white opalescent suspension followed by free drug. Separated niosomes were filled in a dialysis tube to which a sigma dialysis sac was attached to one end. The dialysis tube was suspended in phosphate buffer of pH (7.4), stirred with a magnetic stirrer, and samples were withdrawn at specific time intervals and analysed using high-performance liquid chromatography (HPLC) method.

In vivo Release Study

Albino rats were used for this study. These rats were subdivided with groups. Niosomal sspension used for in vivo study was injected intravenously (through tail vein) using appropriate disposal syringe.

FACTORS AFFECTING FORMATION OF NIOSOMES

Nature of surfactants

A surfactant used for preparation of niosomes must have hydrophilic head and hydrophobic cases single steroidal group[26].The ether type surfactants with single chain alkyl as hydrophobic tail is more toxic than corresponding dialkyletherchain[27]. The ester type surfactants are chemically less stable than ether type surfactants and the former is less toxic than the latter due to ester-linked surfactant degraded by esterases to triglycerides andfatty acid *in vivo*. The surfactants with alkyl chain length from C12-C18 are suitable for preparation of noisome. Surfactants such as $C_{16}EO_5$ (poly-oxyethylene cetyl ether) or $C_{18}EO_5$ (polyoxyethylene steryl ether) are used for preparation of polyhedral vesicles[28].Span series surfactants having HLB number of between 4 and 8 can form vesicles**.**

Structure of surfactants

The geometry of vesicle to be formed from surfactants is affected by its structure, which is related to critical packing parameters. On the basis of critical packing parameters of Surfactants can predicate geometry of vesicle to be formed. Critical packing parameters can be defined using following equation,

CPP (Critical Packing Parameters) = v/lc ×a0

Where v = hydrophobic group volume,, lc = the critical hydrophobic group length,, a0= the area of hydrophilic head group.

From the critical packing parameter value type of miceller structure formed can be ascertained as given below,

If CPP < ½ then formation of spherical micelles,

If ½ < CPP < 1 formation of bilayer micelles,

If CPP > 1 formation inverted micelles.

Membrane composition

The stable niosomes can be prepared with addition of different additives along with surfactants and drugs. Niosomes formed have a number of morphologies and their permeability and stability properties can be altered by manipulating membrane characteristics by different additives. In case of polyhedral niosomes formed from C16G2, the shape of these polyhedral niosome remains unaffected by adding low amount of solulan C24 (cholesteryl poly-24-oxyethylene ether), which prevents aggregation due to development of steric hindrance.In contrast spherical Niosomes are formed by C16G2: cholesterol:solulan (49:49:2). The mean size of niosomes is influenced by membrane composition such as Polyhedral niosomes formed by C16G2: solulan C24 in ratio (91:9) having bigger size (8.0 ± 0.03mm) than spherical/tubular niosomes formed by C16G2: cholesterol:solulan C24 in ratio (49:49:2) (6.6±0.2mm)[29]. Addition of cholesterol molecule to niosomal systemprovides rigidity to the membrane and reduces the leakage of drug from noisome[30].

Nature of encapsulated drug

The physico-chemical properties of encapsulated drug influence charge and rigidity of the niosome bilayer. The drug interacts with surfactant head groups and develops the charge that creates mutual repulsion between surfactant bilayers and hence increases vesicle size[31]. The aggregation of vesicles is prevented due to the charge development on bilayer.

Temperature of hydration

Hydration temperature influences the shape and size of the noisome. For ideal condition it should be above the gel to liquid phase transition temperature of system. Temperature change of niosomal system affects assembly of surfactants into vesicles and also induces vesicle shape transformation. Arunothayanun et al. reported that a polyhedral vesicle formed by C16G2: solulan C24 (91:9) at 25°C which on heating transformed into spherical vesicle at 48°C, but on cooling from 55°C, the vesicle produced a cluster of smaller spherical niosomes at 49°C before changing to the polyhedral structures at 35°C**.** In contrast vesicle formed by C16G2: cholesterol: solulanC24 (49:49:2) shows no shape transformation on heating or cooling. Along with the above mentioned factors, volume of hydration medium and time of hydration of niosomes are also critical factors. Improper selection of these factors may result in formation of fragile niosomes or creation of drug leakage problems.

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THERAPEUTIC APPLICATIONS OF NIOSOMES

Niosomal drug delivery is potentially applicable to many pharmacological agents for their action against various diseases. Some of their therapeutic applications are discussed below.

Targeting of bioactive agents

To reticulo-endothelial system (RES) The cells of RES preferentially take up the vesicles. The uptake of niosomes by the cells is also by circulating serum factors known as opsonins, which mark them for clearance. Such localized drug accumulation has, however, been exploited in treatment of animal tumors known to metastasize to the liver and spleen and in parasitic infestation of liver[32].

To organs other than RES

It has been suggested that carrier system can be directed to specific sites in the body by use of antibodies. Immunoglobulins seem to bind quite readily to the lipid surface, thus offering a convenient means for targeting of drug carrier[33]. Many cells possess the intrinsic ability to recognize and bind particular carbohydrate determinants and this can be exploited to direct carriers system to particular cells.

Neoplasia

Doxorubicin, the anthracyclic antibiotic with broad spectrumanti tumor activity, shows a dose dependant irreversible cardio toxic effect. Niosomal delivery of this drug to mice bearing S-180 tumor increased their life span and decreased the rate of proliferation of sarcoma[34]. Niosomal entrapment increased the half-life of the drug, prolonged its circulation and altered its metabolism. Intravenous administration of methotrexate entrapped in niosomes to S-180 tumor bearing mice resulted in total regression of tumor and also higher plasma level and slower elimination.

Leishmaniasis

Niosomes can be used for targeting of drug in the treatment of diseases in which the infecting organism resides in the organ of reticuloendothelial system. Leishmaniasis is such a disease in which parasite invades cells of liver and spleen. The commonly prescribed drugs are antimonials, which are related to arsenic, and at high concentration they damage the heart, liver and kidney.

The study of antimony distribution in mice, performed by Hunter *et al* showed high liver level after intravenous administration of the carrier forms of the drug.

Delivery of peptide drugs

Yoshida *et al* [35] investigated oral delivery of 9-desglycinamide, 8- arginine vasopressin entrapped in niosomes in an in-vitro intestinal loop model and reported that stability of peptide increased significantly.

Immunological application of niosomes

Niosomes have been used for studying the nature of the immune response provoked by antigens. Brewer and Alexander have reported niosomes as potent adjuvant in terms of immunological selectivity, low toxicity and stability[36].

Niosomes as carriers for Hemoglobin

Niosomes can be used as a carrier for hemoglobin. Niosomal suspension shows a visible spectrum superimposable onto that of free hemoglobin. Vesicles are permeable to oxygen and hemoglobin dissociation curve can be modified similarly to non-encapsulated hemoglobin[37].

Transdermal delivery of drugs by niosomes

Slow penetration of drug through skin is the major drawback of transdermal route of delivery. An increase in the penetration rate has been achieved by transdermal delivery of drug incorporated in niosomes. Jayraman *et al* has studied the topical delivery of erythromycin from various formulations including niosomes or hairless mouse. From the studies, and confocal microscopy, it was seen that non-ionic vesicles could be formulated to target pilosebaceous glands.

CONCLUSION

Niosomal drug delivery systems are an example of one of the various drug delivery systems available. Niosomes appeared to be a well preferred drug delivery system over liposome as niosomes being stable and economic. The technology utilized in niosomes is still greatly in its infancy, and already it is showing promise in the fields of cancer and infectious disease treatments. Niosomes represent a promising drug delivery technology and much research has to be inspired in this to juice out all the potential in this novel drug delivery system.

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